Marked Lability in Urinary Cortisol Levels in Subgroups of Combat Veterans With Posttraumatic Stress Disorder During an Intensive Exposure Treatment Program

JOHN W. MASON, MD, SHEILA WANG, PHD, RACHEL YEHUDA, PHD, HADAR LUBIN, MD, DAVID JOHNSON, PHD, J. DOUGLAS BREMNER, MD, DENNIS CHARNEY, MD, AND STEVEN SOUTHWICK, MD

Objective: The objective of this study was to obtain longitudinal data on lability of cortisol levels in posttraumatic stress disorder (PTSD) because previous studies have largely been based on sampling at a single time point and have yielded varying results. **Methods:** This study measured urinary cortisol levels at admission, midcourse, and discharge during a 90-day hospitalization period in male Vietnam combat veterans with PTSD ($N = 51$). **Results:** Although there were no significant differences in the mean ± SEM urinary cortisol levels between the admission (59.4 ± 3.0 μg/d), midcourse (55.6 ± 3.9 μg/d), and discharge (53.4 ± 3.4 μg/d) values, marked lability of cortisol levels in individual patients was observed over time, with changes ranging from +93 to −58 μg/d from admission to midcourse. In addition, this hormonal lability defined discrete subgroups of patients on the basis of the longitudinal pattern of cortisol change during exposure treatment, and there were significant psychometric differences in the level of social functioning between these subgroups. **Conclusions:** The findings do not support the concept of either a static "hypocortisolism" or "hypercortisolism" in PTSD, but rather suggest a *psychogenic* basis for cortisol alterations in PTSD in relation to psychosocial stress and indicate a central regulatory dysfunction of the hypothalamic-pituitary-adrenal axis characterized by a dynamic tendency to overreact in both upward and downward directions. The longitudinal findings fit with recent observations that cortisol elevations occur when acutely superimposed stressful conditions emotionally engage patients and overwhelm the usually dominating disengaging coping mechanisms associated with suppression of cortisol levels in PTSD. The findings emphasize the importance of longitudinal data in studies of the hypothalamic-pituitary-adrenal axis in PTSD. **Key words:** cortisol, PTSD subtypes, hypothalamic-pituitary-adrenal axis, longitudinal, stress.

BPRS = Brief Psychiatric Rating Scale; CAPS-2 = Clinician-Administered PTSD Scale; DES = Dissociative Experiences Scale; DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders*, third edition revised; HPA = hypothalamic-pituitary-adrenal; MMPI-2 = Minnesota Multiphasic Personality Inventory; PTSD = posttraumatic stress disorder.

INTRODUCTION

Studies of cortisol and HPA axis alterations in combat-related PTSD have so far yielded variable results in terms of the direction of hormonal change. Early studies in which patients were seeking treatment as individuals in a routine hospital psychiatry service setting with a supportive, crisis intervention treatment approach, including shoring up psychological defenses and imposing minimal external demands, showed relatively low cortisol levels (1, 2), whereas later studies in which PTSD patient groups were actively recruited for intensive biological research protocols showed relatively higher mean cortisol levels (3, 4). Except for the original pilot study, which included data at three points during hospitalization (1), limitations of the above early studies of mean values in PTSD patient samples involved the lack of longitudinal design and the dependence on cortisol levels at only a single point in time, which did not permit assessment of how labile cortisol levels might be in this disorder in relation to changes in clinical state and acute psychosocial influences over time.

A recent study of several large samples of PTSD patients during treatment in the National Center for PTSD has suggested the possibility that acute superimposed stress related to the intensity of the research and clinical conditions under which studies are conducted may represent an overlooked confounding independent variable largely accounting for the variability in cortisol findings so far in this field (J. Mason et al., unpublished). This study showed not only relatively high *mean* cortisol levels in all samples, but also considerable *individual differences* in cortisol levels between patients at the same point in time, as judged by a cortisol range of more than 100 μg/d (J. Mason et al., unpublished). Such a large range indicates a substantial degree of clinical heterogeneity within these patient samples representing a single primary diagnostic category.

The question arises, then, of whether such individual differences in the recent National Center for PTSD studies represent stable, enduring differences between "high cortisol" and "low cortisol" PTSD patients who

From the Department of Psychiatry, Yale University School of Medicine, New Haven, and National Center for PTSD, Clinical Neuroscience Division, Veterans Affairs Medical Center, West Haven, CT (J.M., S.W., H.L., D.J., J.D.B., D.C., S.S.); and the Department of Psychiatry, Mount Sinai Medical School, New York, and Bronx Veterans Affairs Hospital, Bronx, NY.

Address reprint requests to: John W. Mason, MD, 32 Maple Vale Drive, Woodbridge, CT 06525. Email: jwmason@pol.net

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tend to maintain their rank order over time or rather possibly reflect episodic fluctuations in clinical state in relation to changing psychosocial influences or stages of illness. Some earlier longitudinal psychoendocrine studies of patients with other major psychiatric disorders established that cortisol levels may change significantly at different points in time in patients with a given diagnosis, apparently in relation to changes in clinical state and in relation to discrete stages of decompensation (5–7).

The purpose of the present study was to measure cortisol levels in a large sample of PTSD patients during hospitalization and treatment over a substantial period of time to determine if such factors as psychosocial stress related to hospital admission or to an intensive exposure treatment program and intensive research protocols might be associated with significant changes in cortisol levels in individual patients.

METHODS

The present longitudinal study involved a total of 51 male Vietnam combat veterans with PTSD who were able to complete the intensive West Haven National Center for PTSD treatment and research program of 90 days duration. They represent a subset of a larger sample of 72 patients in a study comparing mean cortisol levels of multiple PTSD patient samples measured at only a single point in time (J. Mason et al., unpublished).

Characterization of the PTSD Patient Sample

Some detail will be given in characterizing the PTSD patient sample and study conditions because our experience indicates that this may be particularly important for making valid comparisons with previous or future studies from other sources with different samples of PTSD patients. The diagnosis of PTSD was established by means of DSM-III-R criteria on the basis of the Structured Clinical Interview for DSM-III-R (8). Other clinical assessments used in characterizing the patient sample included the Mississippi Scale for Combat-Related PTSD (9), the Clinician-Administered PTSD Scale (CAPS-2) (10), the Combat Exposure Scale (11), the Brief Psychiatric Rating Scale (BPRS) (12), the Dissociative Experiences Scale (DES) (13), and the Minnesota Multiphasic Personality Inventory (MMPI-2) (14).

Mean scores ± SEM for the total sample of 51 patients relating to the severity of PTSD were 133 ± 2.1 for the Mississippi Scale, 30.5 ± 1.1 for the Combat Exposure Scale, 45 ± 1.5 for the CAPS-2 frequency sum, and 36 ± 1.2 for the CAPS-2 intensity sum. The BPRS sum, a broader psychopathology measure, was 21 ± 1.3. The MMPI-2 Content Scale Depression measure (86.4 ± 1.3) and the Mississippi King Numbing-Withdrawal Factor (44.0 ± 0.7) may also be useful in characterizing PTSD patient samples in cortisol studies, for shame-depressive features and emotional numbing or "disengagement" features, respectively (15). From a demographic standpoint, the patient sample was 88% white and 12% black. There was an average age of 42.7 years, weight of 84 kg, and height of 178 cm. With regard to comorbidity in the total sample, DSM-III-R diagnostic criteria were met by 79% for previous alcohol abuse, 40% for major depressive disorder, 25% for polysubstance abuse, and 19% for anxiety disorder.

Exclusion criteria included psychotic disorders, major medical illnesses, hormonal medication, organic brain syndrome, and current drug or alcohol abuse less than 3 months before the study. Urine toxicological screening for substance abuse was done on admission and at intervals during the hospitalization period. About 50% of the patients had been taking some psychiatric medication previously, mostly antidepressants or benzodiazepines, and patients were required to begin withdrawal 3 weeks before entering the protocol and to remain without medication during the study.

All 51 patients were recruited and gave informed consent for participation in a research-oriented inpatient treatment program of about 3 months' duration in the Veterans Affairs National Center for PTSD. Although all of the patients were highly symptomatic and had relatively severe, chronic PTSD, none of the patients was admitted in an acute crisis stage, and all were screened for scheduled admission with a requirement that there was some current level of stability in their life and that their level of social functioning was high enough to enable them to be likely to endure the intensive treatment and research program.

Study Conditions: Selection Factors and Ward Milieu

Selection factors included preference for patients who were judged to be unlikely to create serious ward management problems and who were considered likely to be compliant and able to tolerate and complete the lengthy and demanding treatment and research program. Patients were not required to participate in the various research studies to enter the treatment program. The group-oriented exposure treatment program was designed to deal intensively with both the primary trauma in combat and the secondary trauma related to the return home. The patients were informed well in advance that if possible, they should be free of medication, in some cases for the first time in many years. They knew that they would be involved in community activities and in close and ongoing interactions with other patients within a structured group, as a member of a 12-patient cohort. They knew that they would be expected to disclose their own traumatic experiences and feelings related to Vietnam, in many cases things they had seldom or never confided to anyone in the past. These group "traumatic memory" sessions peaked during the sixth week, just preceding the midcourse point of hospitalization. They also knew that they would be expected to express their feelings concerning their traumatic experiences through writing, drawing, drama, and art.

Despite these requirements, the dropout rate was relatively low, about 13%, and mostly involved patients who lapsed into drug use early in the program. Throughout hospitalization there was an intensive schedule of 32 hours per week of individual and group therapy, as well as demands on patient time for participation in a variety of elective biological or psychological research projects. These methodological details are considered relevant because they obviously relate to the practicability of using coping strategies such as avoidance, withdrawal, or emotional numbing, which are commonly relied on preferentially by many PTSD patients and which have been shown to be associated with lower cortisol levels in a related recent study (15).

Hormonal Measurements

Although the large and complex multi-project and multi-investigator structure of the National Center clinical and research programs, along with the desire to avoid excessive research demands on the patients, did not permit frequent longitudinal hormonal measures, we were able to obtain 24-hour urine samples at three points

in time from all 51 patients: 1) within a period of several days after hospital admission, 2) during the midcourse (sixth week) period of hospitalization near the peak of the intensive traumatic memories group therapy sessions, and 3) within a period of several days before hospital discharge. The urine samples were collected from each patient in 3-liter amber polypropylene bottles and were kept at −20°C in a commercial freezer during the collection period. Completeness of urine collections was monitored by staff observers and by determination of urinary creatinine excretion. Mean daily creatinine level was 1.54 g/d (normal range, 0.8–2.0 g/d).

After standardized, rapid thawing and shaking of the frozen 24-hour urine samples, 2-ml untreated urine aliquots of each sample were saved for the cortisol assays and frozen. All aliquots were kept frozen at −70°C until the hormonal assays were performed about 1 week later. Free cortisol excretion rate was measured using a radioimmunoassay kit obtained from the Incstar Corporation (now Diasporin Corp., Stillwater, MN), which showed an interassay coefficient of variation of 4.0% in our laboratory.

In the analysis of data, statistical comparisons of multiple group mean values were done with a one-way analysis of variance and Duncan's Multiple Range test. For comparisons between two groups, a standard *t* test was used.

RESULTS

Longitudinal Study of Lability of Cortisol Levels During Hospital Course

On analyzing the findings in the total sample of 51 patients, we found that there were no significant differences in the mean ± SEM urinary cortisol levels between the admission (59.4 ± 3.0 μg/d), midcourse (55.6 ± 3.9 μg/d), and discharge (53.4 ± 3.4 μg/d) values. Closer inspection of the raw longitudinal data, however, indicated that these mean values alone are very misleading with regard to some important dynamic features of the underlying individual differences between patients during our period of study.

Figure 1 presents all the raw individual longitudinal data showing the direction and degree of change in urinary cortisol levels between the admission, midcourse, and discharge periods in all 51 patients who were able to tolerate and complete the program. Notice the striking degree of lability in cortisol levels displayed by the great majority of patients between the three time periods, particularly the finding that many patients show a *marked decrease* while many others show the diametrical opposite, a *marked increase*, in cortisol levels from the admission period to the midcourse period. An appreciable number of patients show very substantial cortisol elevations with values even above the 90 μg/d "upper limit of normal" at one or another of the three points in time. Similarly, at the lower end, a number of patients show cortisol levels ranging from 40 to less than 20 μg/d.

These findings raise the question of possible overreactivity of the cortisol system in an upward direction under some conditions as well as in a downward direction. Notice also that the direction of change is not simply dependent on the initial value, but that patients may rise from either a low or high baseline, or fall from a high or low baseline, so that we are not dealing just with a law of initial values effect. Notice also the tendency for most patients to reverse the direction of change from the peak of exposure treatment midcourse point to the discharge period.

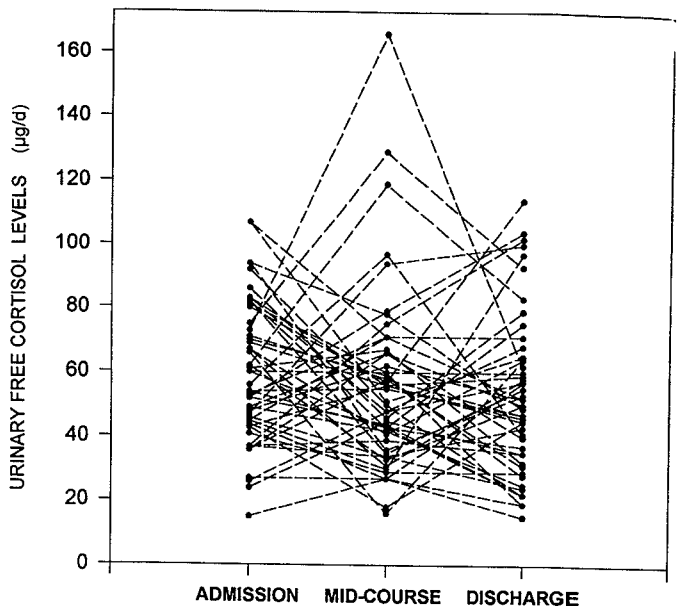

Fig. 1. Marked lability in urinary cortisol levels in individual PTSD inpatients participating in an intensive 3-month treatment and research program in the National Center for PTSD ($N = 51$).

Subgroup Differences in Patterns of Longitudinal Cortisol Change

Figure 2 presents a scatterplot of all the individual patient cortisol "delta" or "change" values from the admission period to the midcourse period (calculated as midcourse value minus admission value), ranging from an increase of +93 μg/d to a decrease of −58 μg/d. Except for the one outlying patient with the +93 μg/d value, the shape of the distribution curve is relatively symmetrical. There is a slightly greater tendency for patients to show decreased rather than increased levels, but the graph shows a substantial number of patients with *marked increases* above +20 μg/d as well as those with *marked decreases* below −20 μg/d. For the purpose of considering the possibility that the direction of cortisol response from the admission to the midcourse period in this setting might reflect important clinical differences between

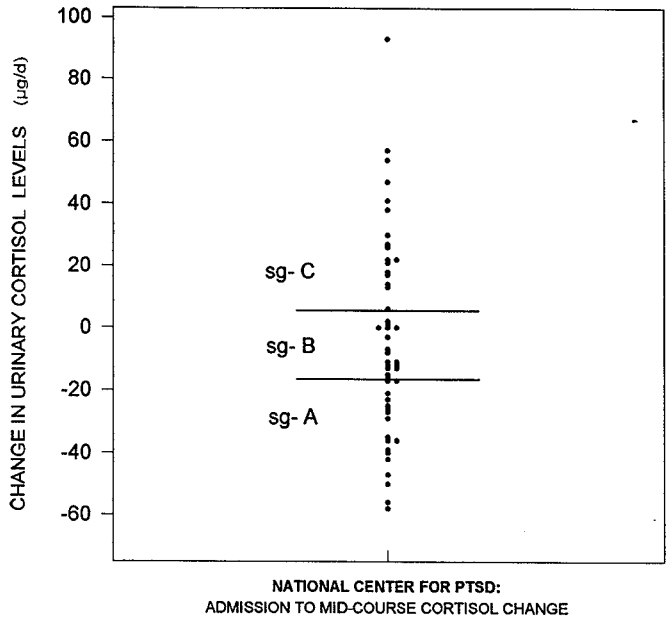

Fig. 2. Direction and magnitude of urinary cortisol level change in individual PTSD inpatients between the period of hospital admission and the midcourse period representing the peak of group and exposure treatment. The delta value was calculated as the midcourse value minus the admission value. Three subgroups (sg-A, sg-B, sg-C) are defined on the basis of dividing the distribution curve into terciles: sg-A = bottom tercile subgroup with greatest decreases; sg-B = middle tercile subgroup with the least amount of changes; sg-C = top tercile with greatest increases.

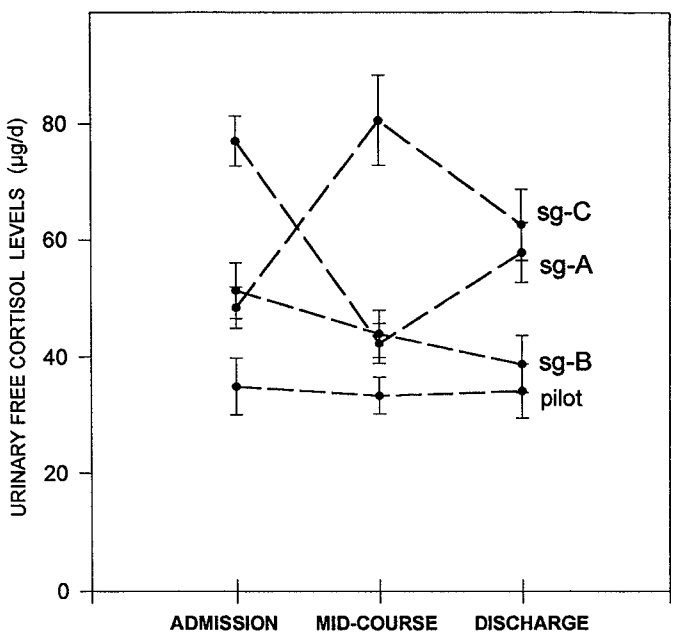

Fig. 3. Marked differences in longitudinal urinary cortisol lability patterns in PTSD patient subgroups participating in an intensive 3-month treatment and research program in the National Center for PTSD. PTSD inpatient subgroups are based on cortisol change from admission to midcourse: sg-A = bottom tercile subgroup with greatest decreases; sg-B = middle tercile subgroup with the least amount of changes; sg-C = top tercile with greatest increases; pilot = pilot study sample involving a much less intensive clinical setting.

patients, the total sample was divided into three subgroups, as shown by the cross-bars in Figure 2. Subgroup A is the bottom tercile, showing the greatest cortisol decreases; subgroup B, the middle tercile, showing the least cortisol changes; and subgroup C, the top tercile, showing the greatest cortisol increases.

Figure 3 presents the mean cortisol curve configurations for all three subgroups, showing the striking, almost mirror-image differences between subgroups A and C. Subgroup A showed a high cortisol level at admission, followed by a marked drop at midcourse. In contrast, subgroup C showed a low cortisol level at admission, followed by a marked rise in relation to exposure treatment. Subgroup B showed a simple modest decline in cortisol levels during the hospitalization period. A one-way analysis of variance revealed that subgroup A was significantly higher than B and C at the admission period ($F(2,50) = 14.45$, $p < .0001$) and that subgroup C was significantly higher than A and B at the midcourse period ($F(2,50) = 16.17$, $p < .0001$).

Psychometric Differences Between the Cortisol-Defined Subgroups

The logical question arises as to whether the substantial lability of cortisol levels in the present study might be explained on the basis of acute superimposed stress factors and patient selection differences, which have been observed in relation to higher mean cortisol values in the National Center for PTSD patient samples (J. Mason et al., unpublished manuscript). We realize that although this seems to be the most likely supposition at this point, any rigorous testing of this interpretation of the clinical meaning of the cortisol findings requires more than situational criteria and must include objective evaluation of relationships between clinical or psychometric differences and hormonal differences in these hormonally defined subgroups.

Because of the restrictions concerning patient access in the National Center for PTSD setting, involving many different investigators and concurrent research projects, we were unable to obtain sufficient psychometric measurements in the midcourse period, which would have made possible direct correlational studies of longitudinal hormonal and clinical changes. One feasible approach, however, that has produced some potentially helpful leads was to screen the psychometric profile of patients in the initial admission period, looking for possible relationships between admission clinical measures of an enduring characterological nature, using the MMPI-2 data (which was available on

all patients), and the subsequent subgroup pattern of cortisol *change* during the treatment period from the admission to the midpoint of hospitalization.

Although the 10 main clinical scales of the MMPI-2 did not discriminate very well between the two subgroups, when the MMPI-2 Content, Harris-Lingoes, and Supplemental scales subscores for subgroups A and C were analyzed by a standard *t* test, a number of significant clinical differences, shown in Table 1, were revealed. These findings seemed to fit in a clinically plausible way with the hormonal findings.

The first category of clinical differences relate to the much poorer level of social functioning in subgroup A, which is evident in seven different measures representing both characterological aspects and past history of social behavior.

The second category involves MMPI-2 psychological factors, which generally reflect greater severity of symptoms in subgroup A, especially such clinical features as poorly controlled anger, persecutory ideas, fears, low self-esteem and shame-depression (15), that are particularly relevant to social functioning. The greater overall severity of PTSD symptoms in subgroup A is also evident in the MMPI-2 Keane PTSD score.

Because the MMPI-2 does not provide any explicit measures of defensive features known to be related to cortisol levels, we inspected the Mississippi PTSD Scale and found that subgroup A may have a greater tendency to use disengagement coping strategies than subgroup C, as shown by a significant difference in the score of the Mississippi Disengagement Factor developed and described in a related article (15). It is also of interest that subgroup A shows a higher dissociation score than subgroup C at a high level of significance ($p < .004$). Because some clinicians view dissociation as a rather severe form of disengagement in a defensive sense, this finding may well fit clinically with the possibility that there is a greater inclination or need for subgroup A to use disengaging coping strategies.

DISCUSSION

The present finding of considerable lability in cortisol levels and markedly different longitudinal patterns in cortisol fluctuations in combat veterans with PTSD under the conditions of exposure to an intensive treatment and research program at the National Center for PTSD may have important conceptual and practical implications for future work in this field. First, it is clear that the present findings call attention to the importance of including *longitudinal* hormonal and clinical assessments in future HPA axis studies of PTSD. Second, the findings also demonstrate the need to give closer attention to clinical *state* changes and to the *psychosocial factors* involved in the clinical treatment approach and setting, as well as to the conditions imposed by the research protocol itself, as potentially confounding independent variables to be considered

TABLE 1. Psychometric Differences Between Cortisol Subgroups A and C as Reflected in Items From the MMPI-2

Item	Subgroup A (mean ± SEM)	Subgroup C (mean ± SEM)	*t*	*P*
MMPI-2 social factors				
Social responsibility	31.6 ± 1.2	37.9 ± 2.3[a]	2.52	<.02
Social alienation	89.7 ± 2.4[a]	80.3 ± 3.7	2.16	<.04
Alienation (self and others)	75.7 ± 2.0[a]	67.6 ± 2.0	2.81	<.008
Family problems	77.4 ± 2.2[a]	67.7 ± 3.5	2.40	<.02
Work interference	86.7 ± 2.1[a]	76.9 ± 3.0	2.74	<.01
Antisocial practices	71.1 ± 2.5[a]	62.6 ± 3.7	1.96	<.06
Dominance	30.9 ± 0.6	33.7 ± 1.3[a]	1.97	<.06
MMPI-2 psychological factors				
Anger	80.9 ± 1.2[a]	73.5 ± 2.4	2.88	<.007
Inhibition of aggression	36.6 ± 1.5	43.8 ± 2.2[a]	2.78	<.009
Need for affection	33.8 ± 1.3	39.7 ± 2.3[a]	2.32	<.03
Cynicism	71.6 ± 2.4[a]	64.9 ± 2.6	1.91	<.06
Persecutory ideas	99.2 ± 4.7[a]	83.3 ± 7.0	1.93	<.06
Fears	67.7 ± 3.7[a]	54.9 ± 2.0	2.90	<.007
Low self-esteem	74.3 ± 2.6[a]	65.7 ± 3.0	2.21	<.03
Depression-shame	90.2 ± 1.7[a]	82.6 ± 2.6	2.53	<.02
Obsessiveness	74.5 ± 2.8[a]	66.1 ± 2.8	2.13	<.04
PTSD severity (Keane)	100.4 ± 1.9[a]	91.8 ± 3.0	2.53	<.01
Other psychometric scores				
Dissociation (DES)	36.3 ± 4.4[a]	17.3 ± 3.8	3.13	<.004
Disengagement (Mississippi Scale)	57.1 ± 1.1[a]	52.8 ± 1.6	2.29	<.03

[a] Indicates the higher value group for each item.

in both the design and the interpretation of research on the HPA axis in PTSD.

Evidence Implicating Psychosocial Factors in Cortisol Lability in PTSD

Although the lack of longitudinal psychometric data to go with the longitudinal cortisol data is an important limitation in the present study, there are several additional sources of complementary background evidence that support the formulation that the marked lability in cortisol levels observed in the current study was most likely related to psychosocial aspects of the intensive clinical and research study conditions in the National Center for PTSD setting.

First, there is the very extensive early background psychoendocrine literature, which has established firmly the general guideline that psychosocial factors are by far the most prevalent and potent influences on the cortisol system and that this hormonal system is exquisitely sensitive to even extremely subtle and ubiquitous everyday psychosocial stimuli, which require careful consideration as potential confounding independent variables in both basic and clinical investigations (16–18).

Second, a companion study of the West Haven National Center for PTSD patient samples showed mean values and individual differences in cortisol levels to be significantly higher than those in a pilot study done in a much less intensive routine hospital psychiatry service setting (J. Mason et al., unpublished manuscript). It is also highly relevant that the original pilot study, which provides the only previously reported longitudinal data on cortisol levels in combat-related PTSD, showed remarkably little lability at three timepoints, with urinary cortisol levels remaining on a virtually flat line at about 34 μg/d throughout the hospitalization period in the much less intensive clinical and research setting (1, 7). Many methodological conditions in the pilot and recent studies by the same principal investigator were constant, and by far the most obvious methodological differences were in the degree of acute superimposed psychosocial stress related to the greater intensity of the treatment program and setting and the large number of demanding research protocols concurrently seeking patient participation in the National Center for PTSD program (Refs. 1 and 7; J. Mason et al., unpublished).

Third, it is very important that a specially designed and dedicated correlational study has revealed a significant inverse relationship between cortisol levels and the effectiveness of using disengagement strategies such as emotional numbing, avoidance, and withdrawal in coping with psychosocial stress, in a sample of 30 National Center for PTSD inpatients. Cortisol levels were higher when levels of disengagement, particularly emotional numbing, were low, but cortisol levels were *lower* when disengagement coping mechanisms were *high* (15), in keeping with earlier psychoendocrine research building on Singer's "engagement-involvement" concept (7, 19–21).

Singer found in 1957 that preoperative patients who showed the highest cortisol levels the day before elective cardiothoracic surgery were those most "engaged" in anticipatory preparation for the life-threatening experience, whereas patients who used disengagement coping strategies like avoidance and denial showed surprisingly low cortisol levels before surgery. These observations contributed to the development of the construct of engagement-involvement as a very undifferentiated state of emotional arousal that seemed to represent the core intrapsychic process associated with responses of the cortisol system to psychosocial stress, a formulation that has been supported repeatedly in subsequent psychoendocrine studies of stress (7, 16, 19–21). This key concept of an engagement-disengagement axis, of a balance between arousal and antiarousal intrapsychic mechanisms as underlying cortisol adjustments to stress, seems worthy of greater attention in further studies in this field, especially in evaluating the possibility that longitudinal cortisol changes in PTSD patients may have a psychogenic basis in relation to changes in clinical state or stage of illness in response to stressful psychosocial factors in intensive clinical and research settings.

Factors Underlying the Subgroup Differences in Longitudinal Cortisol Lability Patterns

The magnitude of the lability of cortisol levels in PTSD patients observed during the hospital experience in the National Center for PTSD study is noteworthy in itself, but the further observation of the striking heterogeneity in the temporal pattern of cortisol lability, which separates the sample into three patient subgroups, may be of even greater clinical interest and raises the question of what clinical features might characterize these hormonally defined subgroups.

From a clinical standpoint it seems that the differences between the two extreme subgroups (A and C) centered on their clinical state at the time of the transitional period around hospital admission and the subsequent change at the midcourse peak of the treatment program. It is noteworthy that it was the *characterological* measures of the MMPI-2 that discriminated these two subgroups, and it is impressive that the distinguishing characteristics fell into two discrete but closely interrelated categories, the level of social func-

tioning and the level of some socially disabling symptoms. In addition, initial symptom measures suggested in a preliminary way that the two subgroups may have differed in the degree to which dissociation and disengagement defenses were prominent clinical features.

The main elements of the preliminary and tentative clinical formulation that we are suggesting as a possible basis for explaining the difference in the longitudinal pattern of cortisol change between subgroups A and C is organized into a concise summary in Table 2. It is our impression from these admission psychometric data that the patients comprising subgroup A, showing the marked mean cortisol increases during the admission period, generally are those characterized clinically by a more severe degree of illness, as reflected in poorer social functioning, poorer work and family functioning, and higher levels of symptoms (including anger, aggression, violent impulses, fear of uncertainty, persecutory ideas, cynicism and mistrust, and shame-proneness), that may well predispose this subgroup of patients to having greater *difficulty with transitions* from a familiar setting to a largely unknown and intensely social setting with many potentially aversive or threatening features.

As familiarity with the new setting develops, however, the patients eventually become relieved of some uncertainties and manage to adapt gradually with their preferred coping strategies of avoidance, withdrawal, or numbing, which lessen the degree to which they are affectively engaged in the situation so that cortisol levels begin to subside. In keeping with the above formulation of Singer concerning engagement as a determinant of cortisol levels, their decline in cortisol levels toward the midcourse, where the exposure treatment program intensity peaks, might also be seen as indicating that they were not as actively "engaged" in the treatment milieu as were the patients in subgroup C. The higher scores in subgroup A for emotional numbing and disengagement coping strategies would fit with this clinical formulation.

On the other hand, it seems that the patients comprising subgroup C, showing relatively low cortisol levels during the admission period, are those with a less severe degree of illness, with lower levels of the socially disabling symptoms listed above for subgroup A, with higher levels of social functioning, self-esteem, dominance, need for affection, and inhibition of aggression. These patients would seem not only to be less likely to find the intensely social setting at the point of hospital admission aversive, but also to be much more likely to become engaged in the treatment program, including the traumatic memory exposure sessions, which peaked at about the midcourse point, when their high mean levels of cortisol were observed.

We find the contrasts in these subgroups extremely meaningful from a clinical standpoint, but the accuracy of our above assumptions in interpreting the clinical meaning and significance of our cortisol findings can, of course, only be established more conclusively in follow-up work.

Hormonal and Clinical Heterogeneity in PTSD Patient Samples

There are clearly practical reasons to explore further the above cortisol-defined subgroup leads in the present study, in view of the way in which heterogeneity of patient samples, even within a specific primary diagnostic category, can represent such major obstacles in clinical psychiatric research. For example, treatment efficacy research in chronic PTSD populations has so far generally yielded very little return in terms of identifying effective pharmacological or behavioral treatment interventions. A major obstacle and complicating factor in such research has been the substantial clinical heterogeneity of PTSD patient samples, which can obscure treatment benefits to a responsive patient subgroup when statistical analyses are applied only to the total patient sample because no objective subtyping criteria are available. The present

TABLE 2. Clinical Hypotheses About the Relationships Between Differences in Psychometric Profiles and Longitudinal Cortisol Patterns During Hospitalization and Treatment in Subgroups A and C

Subgroup	Clinical Hypothesis
A[a]	May be inclined, because of *more severe* symptoms and social dysfunction, to experience greater difficulty with novelty and the *transition* to an uncertain, demanding, group-oriented setting; are also *less able to engage* in the intensive exposure treatment program, but as familiarity with the setting develops and effective *disengaging* coping strategies are worked out in time, cortisol levels are lowered.
C[b]	May be, because of *less severe* symptoms, higher levels of self-esteem, and better social functioning, more capable of coping with novelty and the *transition* to an intensive group-oriented setting and of subsequently *engaging more fully* in the exposure treatment program, including the traumatic memory sessions near the midcourse period, when their cortisol levels have risen markedly.

[a] High initial cortisol level followed by a decrease.
[b] Low initial cortisol level followed by an increase.

cortisol subgroup findings, as well as previously reported findings involving striking T3 alterations (which can define subgroups in PTSD) (22), raise the possibility that PTSD subtypes based on objective hormonal criteria might provide a promising approach to *reducing* heterogeneity and increasing the rigor and productivity of treatment outcome research with this intractable disorder.

It might be added that recent intensive longitudinal psychoendocrine studies by Wang et al. (23) indicate that PTSD patients may go through discrete clinical stages of decompensation and recompensation during the chronic course of this illness, which may also provide a basis for fine-tuning treatment outcome studies with the view that certain therapies may be stage-dependent and that clinical trials might be facilitated by adding stage criteria to diagnostic criteria in the search for effective treatment choices for individual patients.

CONCLUSIONS AND SUGGESTED FUTURE DIRECTIONS

The present finding of marked longitudinal changes in cortisol levels in PTSD patients in an intensive clinical research setting clearly adds impetus to reconceptualizing the meaning of cortisol alterations in this disorder as most likely having a primarily *psychogenic* basis, which must be viewed in relation to the nature and intensity of acute superimposed stress inherent in a psychosocial setting at the time hormonal measurements are being performed. Companion National Center for PTSD studies indicate that the cortisol level is closely linked to the degree to which the defensive capacity of the patient, along with situational factors, make possible the effective use of disengagement coping strategies in the face of superimposed psychosocial stress (Ref. 15; J. Mason et al., unpublished). In particular, the finding in a related psychometric study of PTSD patients of a significant inverse relationship between low cortisol levels and the disengaging defenses of emotional numbing and avoidance lends substantial support to the use of the engagement-disengagement concept as an organizing principle in the interpretation of the present cortisol findings (15). Such an approach is also supported by findings in a recent prospective study of motor vehicle accident–related PTSD showing that *greater* emotional numbing levels predicted *lower* cortisol levels 6 months after the accident (24).

At this stage it should be emphasized that the suggested clinical characterizations of the cortisol-defined subgroups, although based on some psychometric data, are certainly tentative and speculative, but these formulations do seem to be worthy of further study since no other leads or alternative explanations involving nonpsychosocial variables have emerged. With regard to the specific psychosocial features of the clinical and research setting that may be most directly related to cortisol levels, the opportunistic use of acute psychosocial stress episodes might present a useful strategy in future longitudinal studies of hospitalization or treatment periods. In a related study of thyroid function in the West Haven PTSD patients, for example, marked increases in serum T3 levels were observed in six of seven patients in association with a group traumatic memory therapy session in which each patient was able to recount to the cohort his most stressful memory from combat experience. This hormonal finding seems to indicate that these particular group treatment sessions can be intensely stressful for patients who are able to engage and earnestly participate in revealing previously hidden painful memories and in risking ridicule or harsh judgment by the group (22).

At a more general level, the marked lability of cortisol levels demonstrated in the present study does *not* support pursuing the simplistic, polarized conceptualization of a static "hypocortisolemia" vs. a static "hypercortisolemia" in PTSD, but rather supports pursuing the dynamic concept of a more complex regulatory dysfunction of the HPA axis involving a propensity for relatively large swings of cortisol levels, probably in both downward and upward directions. Because the clinical intensity of arousal or intrusive forces can apparently be so great in PTSD, perhaps it should also be expected that *antiarousal* forces of comparable intensity might be mobilized in an effort to maintain the homeostatic balance between opposing forces. Although the range and percentage of change in cortisol levels in individual PTSD patients in the present study seem quite large and indicate *increased reactivity* in comparison to the ranges previously observed in some earlier longitudinal studies of normal human subjects under chronic stress (21, 25, 26), there is a need for updated comparison longitudinal studies of normal subjects using the current cortisol radioimmunoassay method to establish more precisely the degree to which the range of fluctuation in absolute cortisol levels may be increased or overreactive in both directions in PTSD. There is also a need for further longitudinal studies of PTSD patients being treated as routinely admitted individuals in a "refuge" type of treatment setting, with minimal superimposed acute psychosocial stress, to determine if the original pilot study longitudinal findings of stable, unusually low cortisol levels can be confirmed under such a contrasting set of conditions as compared with the current

study (1). The concept of possible increased reactivity of cortisol levels in PTSD is in keeping with chronobiological observations that the pattern of cortisol secretion and regulation seems to reflect an exaggerated sensitization of the HPA axis in PTSD (27).

Finally, emphasis should be given to the methodological implications of the present findings cautioning against attempts to relate the diagnosis of PTSD in a static manner to cortisol levels obtained at a single point in time and calling for greater attention in future HPA axis research on PTSD: 1) to a longitudinal perspective; 2) to changes in clinical state as a reflection of psychosocial factors, including clinical and research study conditions and settings; 3) to exploring psychoendocrine criteria for reduction of patient sample heterogeneity; and 4) to including a broad battery of psychometric measures for both state and characterological measures to assess psychogenic factors relevant to the interpretation of the clinical meaning and significance of alterations in the cortisol system in PTSD.

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